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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
HAYES, R	
ART UNIT	**PAPER NUMBER**
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

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Office Action Summary

Application No.	Applicant(s)
08/803954	Langley et al
Examiner	**Group Art Unit**
Vanyen	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Peri d f r Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 2/9/98.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 1-11, 28-29, 31-32, 34, 37-39 is/are pending in the application.

Of the above claim(s) 34, 38-39 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-11, 28-29, 31-32, 37 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claim(s) 1-11, 28-29, 31-32, 34, 37-39 were ~~are~~ subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 9

☐ Interview Summary, PTO-413

☒ Notice of References Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Acti n Summary

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I, claims 1-11, 28-29, 31-32 & 37, in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)), and is therefore made FINAL.

Claims 34 & 38-39 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to non-elected inventions.

A clean copy of the claims is again requested to prevent future potential problems, because instant pages 100-105 were canceled by amendment D in the parent application.

Double Patenting

2. Applicant is advised that should claim 1 be found allowable, claims 2, 4, 6-7 & 9-10 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Likewise, should claim 8 be found allowable, claims 28-29 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicants are also reminded in that because parent 07/355027 is at the Board of Appeals, and because the Examiner does not currently have access to the pending claims on appeal, a double patenting rejection may be necessitated if the instant claims are directed toward metalloprotease inhibitor protein products.

Claim Rejections - 35 USC § 112

3. Claims 1-11, 28-29, 31-32 & 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the bovine and human TIMP-2 proteins of Figures 1 & 2, respectively, do not reasonably provide enablement for biologically functional equivalents, or undescribed allelic variants of these TIMP-2-like proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification describes a single metalloprotease inhibitor from two distinct species (i.e., bovine and human TIMP-2 of Figures 1 & 2, respectively). No written description of what structurally constitutes any other metalloprotease inhibitor, or biologically functional equivalents or allelic variants of such, is disclosed within the specification.

The specification generally describes pharmaceutical compositions of metalloprotease inhibitors on pages 14-16. However, it is unknown, and not disclosed, how to determine what constitutes an "effective amount" of any metalloprotease inhibitor, including the disclosed bovine or human TIMP-2 molecules, in that no dosages are described for any protein. Moreover, in that

effective treatment of no disease states is sufficiently described in the specification, and because it is not known at what point during the course of the disease that treatment is recommended, nor how the severity of symptoms relate to the efficacy of any metalloprotease inhibitor protein, and because no guidance is provided in the specification on how to determine how, when, or if, administration of even the TIMP-2 proteins of Figures 1 & 2 are appropriate, it is unknown how one skilled in the art can successfully determining when, or if, "treatment" would be "effective", without undue experimentation to determine such. In other words, the parameters that need to be addressed for assaying when effective treatment of any disease state is incomplete or not disclosed. Additionally, no functional assays are disclosed to determine when, or if, any pharmaceutical composition can be successfully used. Thus, because the skilled artisan can not successfully determine if any pharmaceutical application of the instant invention works *in vivo*, combined with the lack of sufficient guidance in the specification on how to make, use, or assess what constitutes an "effective amount" of the structurally uncharacterized metalloprotease inhibitor molecules of claim 1, claim 32 currently merely constitutes an invitation to experiment to discover how to make and use Applicants' invention.

The name "metalloprotease inhibitor or allelic variants thereof" (i.e., as it relates to how it is defined on pages 10 & 12-13 of the specification) additionally does not sufficiently characterize and enable the proteins that are encompassed by the claims, because the inclusion of any analog, or fragment or "deletion analogs, substitution analogs, and addition analogs", or biologically functional equivalents, within the definition of a TIMP-2-like protein molecule sets forth no

structural characterization and little functional characteristics. The general recitation of the name "metalloprotease inhibitor" also encompasses any putative modification, mutations, substitutions, additions, deletions of any metalloprotease inhibitor protein, because no structure is recited in the claims, and which, therefore, encompasses metalloprotease inhibitors with no structural relationship to even the bovine or human TIMP-2 molecules of Figures 1& 2. Moreover, the specification does not teach which particular amino acids are critical for any metalloprotease inhibitor protein's function, nor what structural features distinguishes the claimed protein from any other different TIMP-2-like proteins that are "analogs thereof". The specification also does not describe any different metalloprotease inhibitor molecules, or any specific "analog" of TIMP-2, that possess any of desired biological activity of a metalloprotease inhibitor. Therefore, because it is unknown nor disclosed what amino acid residues can be altered and still maintain the desired activity of the instant invention, the resultant random mutations to a protein with limited characterization would be predicted by the skilled artisan to result in inactive proteins. For example, Rudinger states on page 3 that "it is impossible to attach a unique significance to any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger further states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Thus, the lack of guidance provided in the specification, as to what minimal structural requirements are necessary for TIMP-2 activity, or for any

metalloprotease inhibitor protein, would prevent the skilled artisan from determining whether any metalloprotease inhibitor, or analog thereof, could be made that retains the desired function of the instant invention, because the 3-dimensional conformation of a native protein would be predicted to be adversely altered without undue experimentation to determine otherwise.

4. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and incomplete because it is unknown what is envisioned as the intended use of the pharmaceutical compositions, since none is recited.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-11, 28-29, 31-32 & 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Murray et al.

Murray et al. teach the isolation and partial sequencing of a native bovine metalloprotease inhibitor (i.e., TIMP-2 that is free of other proteins and inherently at least 95% pure; pg. 4158,

Table III; as it relates to claims 1, 3, 5, 9-10, 31 & 37) that has part of the sequence set forth in Figure 2, and also structurally meets the limitations of a "naturally occurring allelic variant as set forth in Figure 2" (i.e., as defined within the specification to include additions, deletions, substitutions, and fragments thereof; as it relates to claims 8 & 28-29). In that the disclosed sequence of Table III inherently constitutes a synthetic peptide, and because the courts have held that when a product (i.e., TIMP-2) in a product-by-process claim (i.e., being synthetic or made recombinantly) is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process (*In re Thorpe.*, 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983)), the limitations of claims 2, 4, 6- 7 & 28-29 are also anticipated by Murray et al. In that the CAB buffer and/or water constitute pharmaceutically acceptable diluents or carriers (pg. 4155, 1st col., *pp* 5-7), and because the polyacrylamide slices of the 23.9 kD band can be used as an adjuvant (pg. 4156, 2nd col.), the limitations of claim 32 are also met. Additionally, in that this band was labeled/stained with silver (pg. 4157, Fig. 5), the limitations of claim 11 are met. Finally, in that pg. 4158 and Table III, describe a naturally occurring human metalloprotease inhibitor isolated from human skin fibroblasts, the "naturally occurring allelic variant as set forth in Figure 2", as defined within the specification to include additions, deletions, substitutions, and fragments thereof, also anticipate claims 1, 3, 8, 9-10, 28-29, 31 & 37.

6. Claims 1-4, 6-11, 28-29, 31-32 & 37 are rejected under 35 U.S.C. 102(e) as being

anticipated by Stetler-Stevenson et al. (US Patent 5,595,885).

Stetler-Stevenson et al. teach the sequencing and cDNA cloning of an immunogenic/ HPLC/affinity chromatography-isolated native human metalloprotease inhibitor (i.e., CSC-21K/TIMP-2, that is free of other proteins and inherently at least 95% pure; cols. 4-8, 10-12, Figs. 5 & 7) that has part or all of the sequence set forth in Figure 2 (i.e., as it relates to claims 1-4, 6-10, 28-29, 31 & 37). It is also noted that the courts have held that when a product (i.e., TIMP-2) in a product-by-process claim (i.e., being synthetic or made recombinantly) is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process (*In re Thorpe.*, 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983). In that water is a pharmaceutically acceptable diluent or carrier, and pharmaceutical compositions are described, for example, in column 16, the limitations of claim 32 are met. In that the PicoTag method was used to label this protein, the limitations of claim 11 are also met (col. 8, lines 16-25).

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RCH

Robert C. Hayes, Ph.D.
May 7, 1998

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER